MICROPRECIPITATION METHOD FOR PREPARING SUBMICRON SUSPENSIONS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority from provisional application Ser. No. 60/258,160 filed Dec. 22, 2000, which is incorporated herein by reference and made a part hereof.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not Applicable.

BACKGROUND OF THE INVENTION

1. Technical Field

The present invention is concerned with the formation of small particles of organic compounds by precipitating the organic compounds in an aqueous medium to form a pre-suspension followed by adding energy to stabilize a coating of the particle or to alter the lattice structure of the particle. The process is preferably used to prepare a suspension of a poorly water-soluble, pharmaceutically active compound suitable for parenteral administration.

2. Background Art

There is an ever increasing number of pharmaceutical drugs being formulated that are poorly soluble or insoluble in aqueous solutions. Such drugs provide challenges to delivering them in an injectable form such as through parenteral administration. Drugs that are insoluble in water can have significant benefits when formulated as a stable suspension of sub-micron particles. Accurate control of particle size is essential for safe and efficacious use of these formulations. Particles must be less than seven microns in diameter to safely pass through capillaries without causing emboli (Allen et al., 1987; Davis and Taube, 1978; Schroeder et al., 1978; Yokel et al., 1981).

One approach to delivering an insoluble drug is disclosed in U.S. Pat. No. 2,745,785. This patent discloses a method for preparing crystals of penicillin G suitable for parenteral administration. The method includes the step of recrystallizing the penicillin G from a formamide solution by adding water to reduce the solubility of the penicillin G. The '785 patent further provides that the penicillin G particles can be coated with wetting agents such as lecithin, or emulsifiers, surface-active and defoaming agents, or partial higher fatty acid esters of sorbitan or polyoxyalkyklene derivatives thereof, or aryl alkyl polyether alcohols or salts thereof. The '785 patent further discloses micronizing the penicillin G with an air blast under pressure to form crystals ranging from about 5 to 20 microns.

Another approach is disclosed in U.S. Pat. No. 5,118,528 which discloses a process for preparing nanoparticles. The process includes the steps of: (1) preparing a liquid phase of a substance in a solvent or a mixture of solvents to which may be added one or more surfactants, (2) preparing a second liquid phase of a non-solvent or a mixture of non-solvents, the non-solvent is miscible with the solvent or mixture of solvents for the substance, (3) adding together the solutions of (1) and (2) with stirring; and (4) removing of unwanted solvents to produce a colloidal suspension of nanoparticles. The '528 patent discloses that it produces particles of the substance smaller than 500 nm without the supply of energy. In particular the '528 patent states that it is undesirable to use high energy equipment such as sonicators and homogenizers.

U.S. Pat. No. 4,826,689 discloses a method for making uniformly sized particles from water-insoluble drugs or other organic compounds. First, a suitable solid organic compound is dissolved in an organic solvent, and the solution can be diluted with a non-solvent. Then, an aqueous precipitating liquid is infused, precipitating non-aggregated particles with substantially uniform mean diameter. The particles are then separated from the organic solvent. Depending on the organic compound and the desired particle size, the parameters of temperature, ratio of non-solvent to organic solvent, infusion rate, stir rate, and volume can be varied according to the invention. The '689 patent discloses this process forms a drug in a metastable state which is thermodynamically unstable and which eventually converts to a more stable crystalline state. The '689 patent discloses trapping the drug in a metastable state in which the free energy lies between that of the starting drug solution and the stable crystalline form. The '689 patent discloses utilizing crystallization inhibitors (e.g., polyvinylpyrrolidinone) and surface-active agents (e.g., poly(oxyethylene)-co-oxypropylene)) to render the precipitate stable enough to be isolated by centrifugation, membrane filtration or reverse osmosis.

In U.S. Pat. Nos. 5,091,188; 5,091,187 and 4,725,442 which disclose (a) either coating small drug particles with natural or synthetic phospholipids or (b) dissolving the drug in a suitable lipophilic carrier and forming an emulsion stabilized with natural or semisynthetic phospholipids. One of the disadvantages of these approaches is they rely on the quality of the raw material of the drug and do not disclose steps of changing the morphology of the raw material to render the material in a friable, more easily processed form.

Another approach to providing insoluble drugs for parenteral delivery is disclosed in U.S. Pat. No. 5,145,684. The '684 patent discloses the wet milling of an insoluble drug in the presence of a surface modifier to provide a drug particle having an average effective particle size of less than 400 nm. The '684 patent discloses the surface modifier is adsorbed on the surface of the drug particle in an amount sufficient to prevent agglomeration into larger particles.

Yet another attempt to provide insoluble drugs for parenteral delivery is disclosed in U.S. Pat. No. 5,922,355. The '355 patent discloses providing submicron sized particles of insoluble drugs using a combination of surface modifiers and a phospholipid followed by particle size reduction using techniques such as sonication, homogenization, milling, microfluidization, precipitation or recrystallization. There is no disclosure in the '355 patent of changing process conditions to make crystals in a more friable for.

U.S. Pat. No. 5,780,062 discloses a method of preparing small particles of insoluble drugs by (1) dissolving the drug in a water-miscible first solvent, (2) preparing a second solution of a polymer and an amphiphile in an aqueous second solvent in which the drug is substantially insoluble whereby a polymer/amphiphile complex is formed and (3) mixing the solutions from the first and second steps to precipitate an aggregate of the drug and polymer/amphiphile complex.

U.S. Pat. No. 5,858,410 discloses a pharmaceutical nanosuspension suitable for parenteral administration. The '410 patent discloses subjecting at least one solid therapeutically active compound dispersed in a solvent to high pressure homogenization in a piston-gap homogenizer to form particles having an average diameter, determined by photon correlation spectroscopy (PCS) of 10 nm to 1000 nm, the